15

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537/182WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17294	29/07/1999	30/07/1998
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant BIOMEASURE INCORPORATED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 16 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/02/2000	21.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/17294

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4.

because:

☒ the said international application, or the said claims Nos. 1-4 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4 (partially), 5 (entirely).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	none
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	5 (yes), 1-4 (see seperate sheet)
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1:	US 4 853 371
D2:	US 5 688 530
D3:	WO 98 08 529
D4:	WO 98 10 786
D5:	US 5 506 339
D6:	Hepatology, vol. 27, no. 4, April 1998, pp. 920-925
D7:	Br. J. Clin. Pharmacol., vol. 41, no. 2, 1996, pp. 109-114
D8:	American Journal of Hospital Pharmacy, vol. 51, no. 1, 1994, pp. 1184-1192
D9:	European Journal of Cancer, vol. 30A, no. 1, 1994, pp. 28-30
D10:	Gastroenterology, vol. 100, no. 5, 1991, p. A448
D11:	Kawasaki Medical Journal, vol. 22, no. 4, 1996, pp. 233-237
D12:	Archives of Dermatology, vol. 131, no. 10, 1995, pp. 1207-1209
D13:	Archives of Diseases in Childhood, vol. 63, no. 12, 1988, pp. 1493-1494
D14:	Hormone Research, vol. 39, nos.5-6, 1993, pp. 207-212
D15:	Revue du Praticien, vol. 46, 1996, pp. 1509-1513
D16:	American Journal of the Medical sciences, vol. 309, no. 6, 1995, pp. 312-314
D17:	Surgery (St Louis), vol. 121, no. 6, 1997, pp. 606-610
D18:	Surgery (St Louis), vol. 118, no. 1, 1995, pp. 87-97
D19:	Clinical Neurology and Neurosurgery, vol. 100, no. 1, March 1998, pp. 40-43
D20:	Journal of Clinical Endocrinology and Metabolism, vol. 70, no. 3, 1990, pp. 661-669
D21:	Journal of Clinical Endocrinology and Metabolism, vol. 83, no. 2, 1998, pp. 339-343
D22:	Pharmacology and Therapeutics, vol. 60, no. 2, 1994, pp. 245-264
D23:	Br. J. Clin. Pharmacol., vol. 43, no. 1, 1997, pp. 65-70
D24:	Surgery, vol. 116, no. 6, 1994, pp. 1139-1147

Section III
Non-establishment of opinion

Claims 1-4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV
Unity

The present application does not comply with the requirements for unity of invention, (Rule 13.1 PCT), the reasons are as follows:

The present IEA agrees with the ISA considering that 6 inventions are presently claimed:

1. Claims 1-5 partially

> Methods for treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of systemic sclerosis, pancreatic pseudocysts and ascites, VIPoma, neisoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal veinous hypertension and complications of portal hypertension, small bowel obstruction and duodengastric reflux.

2. Claims 1-5 partially

> Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of Cushing syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy and Paget's disease.

3. Claims 1-3, 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of meningioma and cancer cachexia.

4. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of psoriasis.

5. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of hypotension.

6. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of panic attacks

The technical problem underlying the present application is the provision of pharmaceutical compositions comprising lanreotide and, using said compound, methods of treating various diseases as recited in claims 1 and 5. Following page 1, lines 11-27 and page 3, lines 20-29 of the description, the solutions provided by the present application fall into six groups:

1: Treatment of gastroenterological diseases, (systemic sclerosis, pancrestic pseudocysts and ascites, VIPoma, neisoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial protal veinous hypertension and complications of portal hypertension, small bowel obstruction and duodengastric reflux).

2: Treatment of endocrinological diseases, (Cushing syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy and Paget's disease).

3: Treatment of cancer (meningioma) and related conditions, (cachexia).
4: Treatment of psoriasis.
5: Treatment of hypotension.
6: Treatment of panic attacks.

The use of lanreotide to treat diseases falling into groups 1-6 above has been described in the prior art:

For diarrhoea, diabetes related retinopathy and cancer, see US 4,853,371, cited in the application, lines 9-32 of col. 4.

For irritable bowel syndrome, diarrhoea, VIPoma, gastrinoma, gastrointestinal bleeding and complications of diabetes, see US 5,688,530, compound f, col. 5 and lines 30-42 of col. 7.

For systemic sclerosis, see WO 98/08529, line 32, page 8 and claims 1,2,6, 29, 38 and 85.

For hyperinsulinism, part of syndrome X of Reaven, see WO 98/107686, lines 13-19, page 1 and lines 11-29, page 4.

For portal veinous hypertension and its complications, see Mottet et al.

For AIDS related diarrhoea, see Sobhani et al.

For hypercalcemia of malignancy, see Anthony et al.

In view of this prior art the technical problem underlying the present application, can be defined as the provision of alternative medical uses of lanreotide for the treatment of various diseases as recited above. Taking into account the disclosure in the prior art of the use of lanreotide to treat some of the diseases, bearing in mind the essential differences among the solutions provided and considering that no other technical features can be acknowledged, which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT, the IEA agrees with the ISA that there is no single inventive concept underlying the plurality of inventions of the

present application in the sense of Rule 13.1 PCT. Consequently there is a lack of unity of invention.

The applicant has had a search report drawn for subject matter relating to groups 1, 2, 3 and 5 as defined above. The applicant has further paid additional examination fees for groups 1, 2, 3 and 5. Thus, this IPER is based on these four groups of inventions.

Section V

V.1. Novelty

Objections under Article 33(2) PCT:

Present claim 5 relates to a pharmaceutical composition comprising the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, (lanreotide) for use in the treatment of different diseases. It this context it is pointed out that the intended purpose of a pharmaceutical composition is not considered to be a technical feature that would distinguish such a composition from any known pharmaceutical preparation comprising the same ingredients. Thus, the subject matter of present claim 5 lacks novelty over existing pharmaceutical preparations comprising the acetate salt of lanreotide. Such compositions are known from several of the documents cited in the search report and a product is even marketed, (cf. present application, page 4, lines 1-2).

GROUP 1, i.e. claims 1-5 partially

Group 1 relates to the use of lanreotide for the treatment of different gastroenterological diseases, (see invitation to pay additional search fees).

Such a use of lanreotide lacks novelty in view of the documents D1-D7 and D23:

D1 discloses the use of lanreotide for treating pancreatitis, diarrhea, ulcer, cancer, diabetes-related retinopathy, diabetes, cirrhosis and hepatitis, (see D1, the passages mentioned in the search report).

D2 discloses the use of the acetate salt of lanreotide for the treatment of gastrointestinal disorders, gastrinoma, gastrointestinal bleeding, irritable bowel syndrome, acute pancreatitis and gastroenteropathic endocrine tumors, (e.g. vipomas),

complications associated with diabetes and cancer, (see D2, the passages mentioned in the search report.)

D3 discloses the use of lanreotide for treating systemic sclerosis and fibrosis of the gastrointestinal system, (see D3, the passages mentioned in the search report).

D4 discloses the use of lanreotide for the treatment of hyperinsulimism, (see D4, the passages mentioned in the search report).

D5 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors, (e.g. vipomas), diabetes and diabetes related pathologies, pancreatitis, ulcers, diarrhea and other diseases, (see D5, the passages mentioned in the search report).

D6 discloses the use of lanreotide in the treatment of postprandial venious hypertension, (see D6, the abstract).

D7 discloses the use of lanreotide for the treatment of diarrhea, (see D7, the passages mentioned in the search report).

D23 discloses the use of lanreotide for the treatment of different gastrointestinal disorders, e.g. pancreatic and bowel fistulas as well as short bowel syndrome, (see D23, the passages mentioned in the search report).

GROUP 2, i.e. claims 1-5 partially

Group 2 relates to the use of lanreotide for the treatment of different endocrinological diseases, (see invitation to pay additional search fees).

Such a use of lanreotide lacks novelty in view of the documents D1, D2, D5 and D14-D16:

D1 discloses the use of lanreotide for treating acromegaly and related hypersecretory endocrine states and in the management of diabetes, (see D1, the passages mentioned in the search report).

D2 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors and complications associated with diabetes, (see D2, the passages mentioned in the search report.)

D5 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors, diabetes and diabetes related pathologies, (see D5, the passages mentioned in the search report).

D14 discloses the use of lanreotide for the treatment of Cushing's syndrome, (see D14, the abstract).

D15 discloses the use of lanreotide for the treatment of gonadotropinomas, (see D15, the abstract and the passages mentioned in the search report).

D16 discloses the use of lanreotide for the treatment of hypercalcemia of malignancy, (see D16, the abstract).

GROUP 3, i.e. claims 1-3, 5 all partially

Group 3 relates to the use of lanreotide for the treatment of meningioma and cancer cachexia, (see invitation to pay additional search fees).

D18 discloses the use of octreotide for the treatment of cancer cachexia, (see D18, the passages mentioned in the search report).

D19 discloses the use of octreotide for the treatment of meningioma, (see D19, the passages mentioned in the search report).

D20 discloses the use of octapeptide analogs of somatostatin for the treatment of neoplasms, in particular meningiomas, (see D20, page 668). Lanreotide does not appear to be explicitly mentioned.

Thus, it appears that the subject matter according to group 3 can be considered novel with respect to the cited documents.

GROUP 5, i.e. claims 1, 2 and 5 all partially

Group 5 relates to the use of lanreotide for the treatment of hypotension, (see invitation to pay additional search fees).

D8, D21 and D23 disclose the use of octerotide for the treatment of hypotension, (see D8, page 1190 and D21, D23 the passages mentioned in the search report).

Thus, since these documents do not disclose the use of lanreotide, it appears that the subject matter according to group 5 can be considered novel with respect to the cited documents.

V.2. Inventive step

Objections under Article 33(3) PCT:

Remarks covering all groups of inventions:

Subject matter, which are not experimentally supported cannot be acknowledged as involving an inventive step. Applicant claims treatment with lanreotide of a very large number of unrelated medical conditions without showing any evidence of any therapeutic effect what so ever. The mere allegation of such therapeutic effects cannot be accepted, (cf. present application, page 5, lines 16-18). Moreover, even if such effects were to be shown, it appears that an inventive step could not be accepted, because it does not appear to be surprising, as applicant alleges, that the well known somatostatin agonist lanreotide shows similar or improved therapeutic effects compared to somatostatin or other analogs, since it appears that this analog has been developed with the aim of improving the therapeutic properties of somatostatin.

Using the "problem/solution approach" when assessing inventive step in the present case also leads to rejection of inventive step, the reasons being as follows: the technical problem can be formulated as provision of novel medical indications for the known somatostatin analog lanreotide. The skilled man would solve this problem by applying lanreotide in the treatment of conditions already known to be treatable with somatostatin or other analogs. Thus, no inventive step can be acknowledged for such medical indications.

GROUP 1, i.e. claims 1-5 partially

Novel subject matter falling within the scope of the present claims relating to group 1 lacks an inventive step, the reasons being as follows: the present application lists all the present medical indications, where somatostatin or agonists of somatostatin have been used, (cf. present application, page 4, line 3 - page 5, line 14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octerotide for the treatment of the presently claimed conditions, (see D8-D13 and D24, the passages mentioned in the search report). Combining any of the documents D8-D13, D24 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostation analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 2, i.e. claims 1-5 partially

Novel subject matter falling within the scope of the present claims relating to group 2 lacks an inventive step, the reasons being as follows: the present application lists all the present medical indications, where somatostatin or agonists of somatostatin have been used, (cf. present application, page 4, line 3 - page 5, line 14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is

that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octerotide for the treatment of the presently claimed conditions, (see D14-D17, the passages mentioned in the search report). Combining any of the documents D14-D17 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostation analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 3, i.e. claims 1-3, 5 all partially

The subject matter of the present claims relating to group 3 lacks an inventive step, the reasons being as follows: the present application lists documents describing the use of somatostatin or agonists of somatostatin for the treatment of meningioma and cancer cachexia, (cf. present application, page 5, lines 12-14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octreotide for the treatment of

the presently claimed conditions, (see D18, which discloses the use of octreotide for the treatment of cancer cachexia, (see D18, the passages mentioned in the search report), D19, which discloses the use of octreotide for the treatment of meningioma, (see D19, the passages mentioned in the search report) and D20, which discloses the use of octapeptide analogs of somatostatin for the treatment of neoplasms, in particular meningiomas, (see D20, page 668)).Thus, combining any of the documents D18-D20 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostatin analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 5, i.e. claims 1, 2 and 5 all partially

The subject matter of the present claims relating to group 5 lacks an inventive step, the reasons being as follows: the present application lists documents describing the use of somatostatin or agonists of somatostatin for the treatment of hypotension, (cf. present application, page 4, lines 32-33). This medical indication is identical to the presently claimed indication. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octreotide for the treatment of the presently claimed condition, (D8, D21 and D23 disclose the use of octreotide for the treatment of hypotension, (see D8, page 1190 and D21, D23 the passages mentioned in the search report).Thus, combining any of the documents D8 or D21 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostatin analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

V.3. Industrial Applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 1-4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI

Certain Documents

The following document may become relevant in the subsequent national/regional phase:

	Priority date:	Filing date:	Publication date:
WO 98 513 32	13.05.97	13.05.98	19.11.98

Section VIII

Objections under Article 5 and 6 PCT:

The present subject matter lacks sufficiency of disclosure in the sense of Article 5 PCT and support in the sense of Article 6 PCT, because the present subject matter, which covers treatment of a large number of different diseases with lanreotide, is not supported in the application. No experimental data what so ever support to alleged therapeutic effects of lanreotide.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

: IRT

To:
FISH & RICHARDSON P.C.
Attn. TSAO,Y.
225 Franklin Street
Boston, Massachusetts 02110-2804
UNITED STATES OF AMERICA

RECEIVED
JUN 2 0 2000
FISH & RICHARDSON, P.C.
BOSTON OFFICE

Docketed By Billing Secretary
Due Date: ______
Deadline: ______
Initials: ______

	Date of mailing *(day/month/year)* 13/06/2000
Applicant's or agent's file reference 00537/182W01	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 99/17294	International filing date *(day/month/year)* 29/07/1999
Applicant BIOMEASURE INCORPORATED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

...stems
resp to rpt 8/13/00
lack of unity 6/28/00
amt (OOP) 9/13/00
Initials: LXA
Record.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nina Vercio

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

1/RA

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TSAO, Y. Rocky
FISH & RICHARDSON P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 21.11.2000
Applicant's or agent's file reference 00537/182WO1	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17294	29/07/1999	30/07/1998

Applicant
BIOMEASURE INCORPORATED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537/182WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17294	29/07/1999	30/07/1998
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant BIOMEASURE INCORPORATED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 16 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/02/2000	21.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/17294

I. **Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4.

because:

☒ the said international application, or the said claims Nos. 1-4 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4 (partially), 5 (entirely).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	none
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	5 (yes), 1-4 (see seperate sheet)
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: US 4 853 371
D2: US 5 688 530
D3: WO 98 08 529
D4: WO 98 10 786
D5: US 5 506 339
D6: Hepatology, vol. 27, no. 4, April 1998, pp. 920-925
D7: Br. J. Clin. Pharmacol., vol. 41, no. 2, 1996, pp. 109-114
D8: American Journal of Hospital Pharmacy, vol. 51, no. 1, 1994, pp. 1184-1192
D9: European Journal of Cancer, vol. 30A, no. 1, 1994, pp. 28-30
D10: Gastroenterology, vol. 100, no. 5, 1991, p. A448
D11: Kawasaki Medical Journal, vol. 22, no. 4, 1996, pp. 233-237
D12: Archives of Dermatology, vol. 131, no. 10, 1995, pp. 1207-1209
D13: Archives of Diseases in Childhood, vol. 63, no. 12, 1988, pp. 1493-1494
D14: Hormone Research, vol. 39, nos.5-6, 1993, pp. 207-212
D15: Revue du Praticien, vol. 46, 1996, pp. 1509-1513
D16: American Journal of the Medical sciences, vol. 309, no. 6, 1995, pp. 312-314
D17: Surgery (St Louis), vol. 121, no. 6, 1997, pp. 606-610
D18: Surgery (St Louis), vol. 118, no. 1, 1995, pp. 87-97
D19: Clinical Neurology and Neurosurgery, vol. 100, no. 1, March 1998, pp. 40-43
D20: Journal of Clinical Endocrinology and Metabolism, vol. 70, no. 3, 1990, pp. 661-669
D21: Journal of Clinical Endocrinology and Metabolism, vol. 83, no. 2, 1998, pp. 339-343
D22: Pharmacology and Therapeutics, vol. 60, no. 2, 1994, pp. 245-264
D23: Br. J. Clin. Pharmacol., vol. 43, no. 1, 1997, pp. 65-70
D24: Surgery, vol. 116, no. 6, 1994, pp. 1139-1147

Section III
Non-establishment of opinion

Claims 1-4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV
Unity

The present application does not comply with the requirements for unity of invention, (Rule 13.1 PCT), the reasons are as follows:

The present IEA agrees with the ISA considering that 6 inventions are presently claimed:

1. Claims 1-5 partially

> Methods for treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of systemic sclerosis, pancreatic pseudocysts and ascites, VIPoma, neisoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal veinous hypertension and complications of portal hypertension, small bowel obstruction and duodengastric reflux.

2. Claims 1-5 partially

> Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of Cushing syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy and Paget's disease.

3. Claims 1-3, 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of meningioma and cancer cachexia.

4. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of psoriasis.

5. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of hypotension.

6. Claims 1, 2 and 5 all partially

Method of treatment using lanreotide and pharmaceutical compositions comprising lanreotide acetate for the treatment of panic attacks

The technical problem underlying the present application is the provision of pharmaceutical compositions comprising lanreotide and, using said compound, methods of treating various diseases as recited in claims 1 and 5. Following page 1, lines 11-27 and page 3, lines 20-29 of the description, the solutions provided by the present application fall into six groups:

1: Treatment of gastroenterological diseases, (systemic sclerosis, pancrestic pseudocysts and ascites, VIPoma, neisoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial protal veinous hypertension and complications of portal hypertension, small bowel obstruction and duodengastric reflux).

2: Treatment of endocrinological diseases, (Cushing syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy and Paget's disease).

3: Treatment of cancer (meningioma) and related conditions, (cachexia).
4: Treatment of psoriasis.
5: Treatment of hypotension.
6: Treatment of panic attacks.

The use of lanreotide to treat diseases falling into groups 1-6 above has been described in the prior art:

For diarrhoea, diabetes related retinopathy and cancer, see US 4,853,371, cited in the application, lines 9-32 of col. 4.

For irritable bowel syndrome, diarrhoea, VIPoma, gastrinoma, gastrointestinal bleeding and complications of diabetes, see US 5,688,530, compound f, col. 5 and lines 30-42 of col. 7.

For systemic sclerosis, see WO 98/08529, line 32, page 8 and claims 1,2,6, 29, 38 and 85.

For hyperinsulinism, part of syndrome X of Reaven, see WO 98/107686, lines 13-19, page 1 and lines 11-29, page 4.

For portal veinous hypertension and its complications, see Mottet et al.

For AIDS related diarrhoea, see Sobhani et al.

For hypercalcemia of malignancy, see Anthony et al.

In view of this prior art the technical problem underlying the present application, can be defined as the provision of alternative medical uses of lanreotide for the treatment of various diseases as recited above. Taking into account the disclosure in the prior art of the use of lanreotide to treat some of the diseases, bearing in mind the essential differences among the solutions provided and considering that no other technical features can be acknowledged, which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT, the IEA agrees with the ISA that there is no single inventive concept underlying the plurality of inventions of the

present application in the sense of Rule 13.1 PCT. Consequently there is a lack of unity of invention.

The applicant has had a search report drawn for subject matter relating to groups 1, 2, 3 and 5 as defined above. The applicant has further paid additional examination fees for groups 1, 2, 3 and 5. Thus, this IPER is based on these four groups of inventions.

Section V

V.1. Novelty

Objections under Article 33(2) PCT:

Present claim 5 relates to a pharmaceutical composition comprising the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, (lanreotide) for use in the treatment of different diseases. It this context it is pointed out that the intended purpose of a pharmaceutical composition is not considered to be a technical feature that would distinguish such a composition from any known pharmaceutical preparation comprising the same ingredients. Thus, the subject matter of present claim 5 lacks novelty over existing pharmaceutical preparations comprising the acetate salt of lanreotide. Such compositions are known from several of the documents cited in the search report and a product is even marketed, (cf. present application, page 4, lines 1-2).

GROUP 1, i.e. claims 1-5 partially

Group 1 relates to the use of lanreotide for the treatment of different gastroenterological diseases, (see invitation to pay additional search fees).

Such a use of lanreotide lacks novelty in view of the documents D1-D7 and D23:

D1 discloses the use of lanreotide for treating pancreatitis, diarrhea, ulcer, cancer, diabetes-related retinopathy, diabetes, cirrhosis and hepatitis, (see D1, the passages mentioned in the search report).

D2 discloses the use of the acetate salt of lanreotide for the treatment of gastrointestinal disorders, gastrinoma, gastrointestinal bleeding, irritable bowel syndrome, acute pancreatitis and gastroenteropathic endocrine tumors, (e.g. vipomas),

complications associated with diabetes and cancer, (see D2, the passages mentioned in the search report.)

D3 discloses the use of lanreotide for treating systemic sclerosis and fibrosis of the gastrointestinal system, (see D3, the passages mentioned in the search report).

D4 discloses the use of lanreotide for the treatment of hyperinsulimism, (see D4, the passages mentioned in the search report).

D5 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors, (e.g. vipomas), diabetes and diabetes related pathologies, pancreatitis, ulcers, diarrhea and other diseases, (see D5, the passages mentioned in the search report).

D6 discloses the use of lanreotide in the treatment of postprandial venious hypertension, (see D6, the abstract).

D7 discloses the use of lanreotide for the treatment of diarrhea, (see D7, the passages mentioned in the search report).

D23 discloses the use of lanreotide for the treatment of different gastrointestinal disorders, e.g. pancreatic and bowel fistulas as well as short bowel syndrome, (see D23, the passages mentioned in the search report).

GROUP 2, i.e. claims 1-5 partially

Group 2 relates to the use of lanreotide for the treatment of different endocrinological diseases, (see invitation to pay additional search fees).

Such a use of lanreotide lacks novelty in view of the documents D1, D2, D5 and D14-D16:

D1 discloses the use of lanreotide for treating acromegaly and related hypersecretory endocrine states and in the management of diabetes, (see D1, the passages mentioned in the search report).

D2 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors and complications associated with diabetes, (see D2, the passages mentioned in the search report.)

D5 discloses the use of the acetate salt of lanreotide for the treatment of endocrine tumors, diabetes and diabetes related pathologies, (see D5, the passages mentioned in the search report).

D14 discloses the use of lanreotide for the treatment of Cushing's syndrome, (see D14, the abstract).

D15 discloses the use of lanreotide for the treatment of gonadotropinomas, (see D15, the abstract and the passages mentioned in the search report).

D16 discloses the use of lanreotide for the treatment of hypercalcemia of malignancy, (see D16, the abstract).

GROUP 3, i.e. claims 1-3, 5 all partially

Group 3 relates to the use of lanreotide for the treatment of meningioma and cancer cachexia, (see invitation to pay additional search fees).

D18 discloses the use of octreotide for the treatment of cancer cachexia, (see D18, the passages mentioned in the search report).

D19 discloses the use of octreotide for the treatment of meningioma, (see D19, the passages mentioned in the search report).

D20 discloses the use of octapeptide analogs of somatostatin for the treatment of neoplasms, in particular meningiomas, (see D20, page 668). Lanreotide does not appear to be explicitly mentioned.

Thus, it appears that the subject matter according to group 3 can be considered novel with respect to the cited documents.

GROUP 5, i.e. claims 1, 2 and 5 all partially

Group 5 relates to the use of lanreotide for the treatment of hypotension, (see invitation to pay additional search fees).

D8, D21 and D23 disclose the use of octerotide for the treatment of hypotension, (see D8, page 1190 and D21, D23 the passages mentioned in the search report).

Thus, since these documents do not disclose the use of lanreotide, it appears that the subject matter according to group 5 can be considered novel with respect to the cited documents.

V.2. Inventive step

Objections under Article 33(3) PCT:

Remarks covering all groups of inventions:

Subject matter, which are not experimentally supported cannot be acknowledged as involving an inventive step. Applicant claims treatment with lanreotide of a very large number of unrelated medical conditions without showing any evidence of any therapeutic effect what so ever. The mere allegation of such therapeutic effects cannot be accepted, (cf. present application, page 5, lines 16-18). Moreover, even if such effects were to be shown, it appears that an inventive step could not be accepted, because it does not appear to be surprising, as applicant alleges, that the well known somatostatin agonist lanreotide shows similar or improved therapeutic effects compared to somatostatin or other analogs, since it appears that this analog has been developed with the aim of improving the therapeutic properties of somatostatin.

Using the "problem/solution approach" when assessing inventive step in the present case also leads to rejection of inventive step, the reasons being as follows: the technical problem can be formulated as provision of novel medical indications for the known somatostatin analog lanreotide. The skilled man would solve this problem by applying lanreotide in the treatment of conditions already known to be treatable with somatostatin or other analogs. Thus, no inventive step can be acknowledged for such medical indications.

GROUP 1, i.e. claims 1-5 partially

Novel subject matter falling within the scope of the present claims relating to group 1 lacks an inventive step, the reasons being as follows: the present application lists all the present medical indications, where somatostatin or agonists of somatostatin have been used, (cf. present application, page 4, line 3 - page 5, line 14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octerotide for the treatment of the presently claimed conditions, (see D8-D13 and D24, the passages mentioned in the search report). Combining any of the documents D8-D13, D24 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostation analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 2, i.e. claims 1-5 partially

Novel subject matter falling within the scope of the present claims relating to group 2 lacks an inventive step, the reasons being as follows: the present application lists all the present medical indications, where somatostatin or agonists of somatostatin have been used, (cf. present application, page 4, line 3 - page 5, line 14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is

that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octerotide for the treatment of the presently claimed conditions, (see D14-D17, the passages mentioned in the search report). Combining any of the documents D14-D17 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostation analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 3, i.e. claims 1-3, 5 all partially

The subject matter of the present claims relating to group 3 lacks an inventive step, the reasons being as follows: the present application lists documents describing the use of somatostatin or agonists of somatostatin for the treatment of meningioma and cancer cachexia, (cf. present application, page 5, lines 12-14). These medical indications are identical to the presently claimed indications. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octreotide for the treatment of

the presently claimed conditions, (see D18, which discloses the use of octreotide for the treatment of cancer cachexia, (see D18, the passages mentioned in the search report), D19, which discloses the use of octreotide for the treatment of meningioma, (see D19, the passages mentioned in the search report) and D20, which discloses the use of octapeptide analogs of somatostatin for the treatment of neoplasms, in particular meningiomas, (see D20, page 668)).Thus, combining any of the documents D18-D20 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostatin analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

GROUP 5, i.e. claims 1, 2 and 5 all partially

The subject matter of the present claims relating to group 5 lacks an inventive step, the reasons being as follows: the present application lists documents describing the use of somatostatin or agonists of somatostatin for the treatment of hypotension, (cf. present application, page 4, lines 32-33). This medical indication is identical to the presently claimed indication. Thus, the difference between the prior art cited in the application and the presently claimed subject matter is that lanreotide is used instead of somatostatin or agonists of somatostatin. However, the use of a well known agonist; namely lanreotide, which is known to be advantageous compared to somatostatin due to inter alia it longer duration of action, for the treatment of conditions known to be treatable with somatostatin or other agonists of somatostatin is not considered to involve an inventive step.

Moreover, many documents teach the use of lanreotide (BIM-23014) as equivalents for somatostatin or octreotide, (see e.g. D22 and D23, the passages mentioned in the search report) and many documents describe the use of octreotide for the treatment of the presently claimed condition, (D8, D21 and D23 disclose the use of octreotide for the treatment of hypotension, (see D8, page 1190 and D21, D23 the passages mentioned in the search report).Thus, combining any of the documents D8 or D21 with any of the documents D22 or D23 leads to the present subject matter.

It can also not be considered to be inventive to use the acetate salt of lanreotide instead of lanreotide or instead of other somatostatin analogs, because the acetate salt as well as other salts are known to be equivalents to lanreotide, (see e.g. D1, the abstract, D2, col. 7, lines 14-29, D3, claim 86, D5, col. 3, lines 13-35 etc).

V.3. Industrial Applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 1-4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI

Certain Documents

The following document may become relevant in the subsequent national/regional phase:

	Priority date:	Filing date:	Publication date:
WO 98 513 32	13.05.97	13.05.98	19.11.98

Section VIII

Objections under Article 5 and 6 PCT:

The present subject matter lacks sufficiency of disclosure in the sense of Article 5 PCT and support in the sense of Article 6 PCT, because the present subject matter, which covers treatment of a large number of different diseases with lanreotide, is not supported in the application. No experimental data what so ever support to alleged therapeutic effects of lanreotide.